The Effect of Pioglitazone on the Alzheimer's Disease

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Abstract
Recent evidence has indicated that type 2 diabetes mellitus (T2DM) increases the risk of developing Alzheimer's disease (AD). AD is a common neurodegenerative disease characterized clinically by progressive deterioration of memory, and pathologically by histopathological changes including extracellular deposits of beta-amyloid (Aβ) peptides forming senile plaques (SP) and the intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau in the brain. Some studies indicate that improving diabetes with appropriate of drug treatment can delay or prevent AD pathology. Pioglitazoneis was a agonist of nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ), exert potent anti-inflammatory effects in the central nervous system and seem to exert neuroprotective effects in vitro. Metaanalysis studies showed that pioglitazone treatment might be therapeutically beneficial in early stages of AD and for patients with mild-to-moderate AD. Further analysis of these studies showed a significant reduction in amyloid beta and tau pathology measured in cerebral blood flow samples from AD patients. Preclinical and clinical studies have evaluated the possible neuroprotective mechanisms of pioglitazone in AD, with some promising results. Here, we will review effect of pioglitazone in Alzheimer's disease.

Keywords*: Alzheimer's Disease, Alzheimer's Dementia, Pioglitazone, Efficacy*

I. INTRODUCTION

Dementia is defined as a clinical syndrome characterized by the development of multiple cognitive deficits that are severe enough to interfere with daily functioning, including social and professional functioning. The cognitive deficits include memory impairment and at least one of the other cognitive domains, such as aphasia (typically, word-finding difficulty), apraxia (inability to perform motor tasks, such as cutting a loaf of bread, despite intact motor function), agnosia (inability to recognize objects), or disturbances in executive functioning (poor abstraction, mental flexibility, planning, and judgment). Dementia rates are growing at alarming proportion in all regions of the world and are related to population aging (Xu, Ferrari, & Wang, 2013) (Harper, Johnston, & Landefeld, 2018). The World Alzheimer Report 2015 estimated that 46.8 million people worldwide are living with dementia in 2015. This number will almost double every 20 years to 74.7 million in 2030 and 131.5 million in 2050 (Prince, Wimo, Ali, Wu, & Prina, 2015).

Alzheimer's disease (AD) is the main cause of dementia (estimated 60-80% of cases), and one of the great health-care challenges of the 21st century (Scheltens, et al., 2016). AD is a common neurodegenerative disease characterized clinically by progressive deterioration of memory, and pathologically by histopathological changes including extracellular deposits of beta-amyloid (Aβ) peptides forming senile plaques (SP) and the intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau in the brain (Dong, Duan, Hu, & Zhao, 2012). Difficulty remembering recent conversations, names or events is often an early clinical symptom; apathy and depression are also often early symptoms. Later symptoms include impaired communication, disorientation, confusion, poor judgment, behavior changes and, ultimately, difficulty speaking, swallowing and walking (Anonymous, 2017). AD is multifactorial disorder that is determined by genetic and environmental as well as their interactions (Xu, Ferrari, & Wang, 2013). Several recent studies suggest that AD could be a degenerative metabolic disease, caused by relevant physiological alterations like diabetes, hypercholesterolemia, and metabolic syndrome (Perez & Quintanilla, 2015).

A potential link between diabetes and cognitive impairment was first reported more than 80 years ago. There is substantial evidence suggesting that type 2 diabetes is associated with cognitive impairment involving both memory and executive function. Several large longitudinal population-based studies have also shown that the rate of cognitive decline is accelerated in elderly people with type 2 diabetes (Xu, Ferrari, & Wang, 2013). However, the mechanisms underlying this association have not been clearly established. Studies have shown that insulin resistance or deficiency alters Aβ and tau protein phosphorylation which lead to the onset of AD. Some studies indicate that improving diabetes can delay or prevent AD pathology, and therefore prevention and control of diabetes may reduce the risk of Mild cognition impaired (MCI) and AD later in life (Song, Bischoff, Song,

Uyemura, & Yamaguchi, 2017). Recent evidence suggests that the choice of drug treatment may influence the risk for patients with diabetes to develop AD. In fact, new findings of Heneka and colleagues suggest that medication with pioglitazone is associated with a lower risk of dementia for T2DM patients, when these are compared to patients treated with metformin or insulin (Perez & Quintanilla, 2015).

Pioglitazone is a agonist of nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ), resolve insulin resistance and are approved medications for type 2 diabetes treatment (Desouza & Shivaswamy, 2010). Pioglitazone exert potent anti-inflammatory effects in the central nervous system and seem to exert neuroprotective effects in vitro. Recently, metaanalysis studies showed that pioglitazone treatment might be therapeutically beneficial in early stages of AD and for patients with mild-to-moderate AD. Further analysis of these studies showed a significant reduction in amyloid beta and tau pathology measured in cerebral blood flow samples from AD patients (Perez & Quintanilla, 2015). In this review, we will discuss the effect of pioglitazone in Alzheimer's disease.

II. PIOGLITAZONE

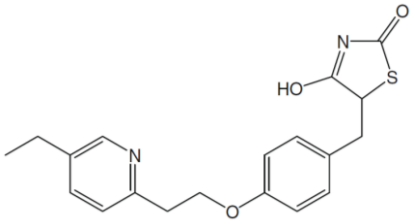

Figure 1. Structure of pioglitazone (Geldenhuys, Funk, Barnes, & Carroll, 2010)

Pioglitazone is an insulin sensitizer of the thiazolidinedione class. It is a peroxisome proliferator-activated receptor (PPARγ) agonist that increases transcription of insulin-responsive genes and thus increases insulin sensitivity. Pioglitazone ameliorates insulin resistance associated with Type 2 diabetes without stimulating insulin release from pancreatic β-cells, thus lowering the risk of hypoglycaemia (Budde, et al., 2003).

Previous clinical trials in healthy subjects have shown that pioglitazone is well absorbed after oral administration. At doses ranging from 2 to 60 mg, peak concentrations of pioglitazone in the blood of healthy subjects are achieved approximately 1.5 h after oral drug administration. Pioglitazone is highly bound to plasma proteins (approximately 97%), with a low tissue distribution and slow elimination (half-life approximately 9 h). Pioglitazone is extensively metabolized in the liver, with the majority excreted as inactive metabolites in the faeces. Pioglitazone undergoes significant hepatic metabolism by hydroxylation of aliphatic methylene groups to form three metabolites (M-I, M-II, and M-IV), by the oxidation of the methyl group to form an additional metabolite (M-V), and by oxidation of metabolite M-IV to metabolite M-VI. The potency of the triglyceride-lowering effect of M-II is nearly twice that of the parent compound, while the potency of metabolites M-III and M-IV is slightly less than that of pioglitazone. The major active metabolites M-III and M-IV have considerably longer terminal half-lives than the parent compound (approximately 26–28 h). Because elimination of pioglitazone and its metabolites is primarily hepatic, pioglitazone may have potential value in patients with Type 2 diabetes who have renal impairment (Budde, et al., 2003).

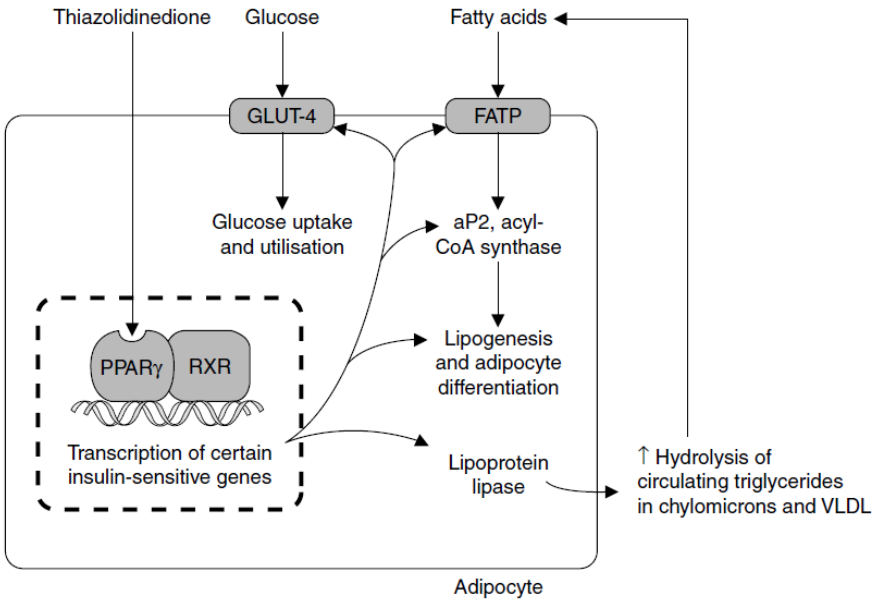

Figure 2. The cellular mechanism of action of pioglitazone (Krentz & Bailey, 2005)

The precise molecular actions of pioglitazone remain to be clarified. Pioglitazone bind to and activate a nuclear receptor (peroxisome proliferator-activated receptor-*γ* [PPAR-*γ*]), which is expressed in many insulin-sensitive tissues, including adipose (major site), skeletal muscle, and liver tissue. PPAR-*γ* regulates transcription of genes that influence glucose and lipid metabolism (Kroon & Williams, 2013). In the cell, PPARγ forms a heterodimer with the retinoid X receptor (RXR). When induced by pioglitazone, a conformational change occurs in the heterodimer and co-repressor complexes are displaced. This promotes binding of the PPARγ–RXR complex to PPARγ response elements (PPRE) in target genes and alteration of the transcription of these genes (Figure 2). PPREs are found in a number of genes involved in lipid metabolism and energy balance, including those encoding for lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid binding protein, fatty acyl- CoA synthase, malic enzyme, glucokinase and the GLUT4 glucose transporter (Hauner, 2002).

In the brain, PPARγ is localized to neurons and astrocytes, where it is involved in the regulation of cell survival and inflammatory responses. Studies have shown that PPARγ is linked to reduced levels of inducible nitric oxide synthase expression and microglial activation in the brain. Experimental data have pointed out that pioglitazone is able to delay Alzheimer's development and promote cell survival through PPARγ activation (Zolezzi & Inestrosa, 2013). Through PPARγ activation, pioglitazone inhibit Aβ – stimulated proinflammatory responses and neurotoxicity (Chou, Ho, & Yang, 2017). In preclinical studies, pioglitazone has been shown to ameliorate AD-related pathology, probably reducing the expression of inflammatory genes and decreasing amyloid plaque burden. It seem to exhibit neuroprotective effects modulating calcium homeostasis in the hippocampus (Femminella, et al., 2017).

III. THE EFFECT OF PIOGLITAZONE ON THE ALZHEIMER'S DISEASE

A. Pioglitazone and Amyloid Clearance

The accumulation of the protein fragment Aβ (called beta-amyloid plaques) outside neurons and the accumulation of an abnormal form of the protein tau (called tau tangles) inside neurons are two of several brain changes associated with AD. Beta-amyloid plaques are believed to contribute to cell death by interfering with neuron-to-neuron communication at synapses, while tau tangles block the transport of nutrients and other essential molecules inside neurons (Anonymous, 2017). Aβ is a protein of 39–42 amino acids that is derived proteolytically from a larger transmembrane protein, amyloid precursor protein (APP), when APP is cleaved by β and γ secretases. The normal function of the Aβ peptides remains uncertain. APP has neurotrophic and neuroprotective properties (Seeley & Miller, 2015). An imbalance between the production and clearance of Aβ is a very early (and often initiating) factor in AD (Wang, Gu, Masters, & Wang, 2017). Interestingly, several studies have shown that treatment with pioglitazone in animal models of AD decreases the Aβ accumulation (Perez & Quintanilla, 2015).

In recent study, the treatment with pioglitazone has been shown to reduce glial pro-inflammatory activity and, to decrease Aβ peptide levels due to the phagocytic activity of microglia (Zhang, et al., 2016). Another preclinical study by Fernandez-Martos and co-workers reported that the association of pioglitazone with leptin showed beneficial effects on the preclinical APPswe/PS1dE9 mice model of familial AD improving cognition and decreasing Aβ levels (Fermandes-Martos, Atkinson, Chuah, KIng, & Vickers, 2016). A Study demonstrated that pioglitazone reduced Aβ42 deposition associated with AKT/GSK3β activation in rats brain,by increasing the levels of insulin-degrading enzyme (IDE) and PPARγ expression. (Yang, et al., 2017).

Treatment of microglia and astrocytes with pioglitazone increased the intracellular degradation of soluble Aβ in a dose-dependent manner. This can occur because pioglitazone induce the overexpression of ApoE helping in the amyloid clearance (Colucci, Karlo, & Landreth, 2012). Also, studies on primary microglial cell cultures showed that pioglitazone induces the activation of PPARγ and the receptor heterodimerization with retinoic X receptor α (RXRα) regulating the expression of CD36, which induced Aβ clearance mediated for phagocytosis (Yamanaka, et al., 2012). Interestingly, a study performed on APP/PS1 mice of 6 and 12 months of age showed that treatment with pioglitazone increased the levels of ATP-binding cassette transporter (ABCA1) and apoE and reduced the soluble and insoluble levels of Aβ by 50% (Colucci, Karlo, & Landreth, 2012).

B. Pioglitazone and Neuroinflammation

Alzheimer's disease is characterized by local inflammatory response in the brain. Main stimulants of inflammation in the brains of AD sufferers consist mainly of damaged neurons and neuritis, neurofibrillary tangles and extremely insoluble Aβ peptide deposits. These stimuli exist from the onset to terminal stages of AD. Thus, neuroinflammation in AD is a major contributor to the AD pathogenesis (Mushtaq, Khan, Kumosani, & Kamal, 2015). Pioglitazone as agonist of nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) has been shown to have a potent anti-inflammatory effect (Perez & Quintanilla, 2015), where PPARγ activity related to oxidative stress response and direct prooxidant as well as antioxidant activity have been described. Interaction with several antioxidant and antiinflammatory regulatory pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), nuclear factor erythroid 2-related factor (NRF2), or the Wnt/β-catenin pathway, have also been noted (Zolezzi & Inestrosa, 2013).

Recently, the effects of pioglitazone against neuroinflammation in animal and brain cell models have been investigated. The treatment with pioglitazone reduced astrocytes and microglial activation in the cortex and hippocampus of the A/T mouse that overproduces Aβ and TGF-β1. A similar study, in which pioglitazone was administrated by oral way, showed a significant inhibition of the IL-6 and TNFα increased levels induced by Aβ stimulation. Additionally, in the Cdk5 conditional knockout mice that showed activation of microglia and astrocytes, pioglitazone treatment resulted in a significant reduction in the activation of microglia and astrocytes and neuronal loss associated with a better survival rate. This is important, because Cdk5 is a protein kinase, whose deregulation contributes to synaptic loss and tau hyperphosphorylation in the AT8 epitope (present in the AD brain) after stimulation of Aβ fibrils. All these studies indicate that inhibition of inflammatory response is involved in the beneficial roles of pioglitazone treatment in AD, and this response is mediated by microglia and astrocytes (Perez & Quintanilla, 2015).

C. Pioglitazone and Mitochondrial Function

It has been reported that mitochondrial abnormalities correlate with dystrophic neurites, the loss of dendritic branches and the pathological alteration of the dendritic spines present in the brains of AD cases. Swerdlow and Khan proposed the mitochondrial cascade hypothesis to explain late-onset, sporadic AD, stating that Aβ deposition, neurofibrillary tangle formation and neurodegeneration are consequent events of mitochondria malfunctioning (Santos, et al., 2010). Mechanisms involved in Aβ neurotoxicity is mediated by oxidative stress and through induction of mitochondrial dysfunction that further leads to oxidative damage by an increased production of reactive oxygen species (ROS) (Zolezzi & Inestrosa, 2013). Oxidative stress is a relative increase in the ratio of free radicals to antioxidants, where the activities of the antioxidant enzymes superoxide dismutase and catalase are significantly decreased in the frontal and temporal cortex of AD patients. Not only that, antioxidant enzyme activity was shown to be spatially correlated with markers of lipid peroxidation (i.e. oxidative damage) and the brain areas particularly affected by neuronal loss in AD. However, increased antioxidant activity in AD brains in response to increased free radical generation has also been reported (Ortiz, Brizuela, Moises, & Merino, 2011).

PPAR activation by pioglitazone has proven to reduce oxidative damage through the reduction of ROS production in several tissues, including the brain, liver, and blood vessels, among others, due to the interaction of PPARs with antiinflammatory pathways such as NF-κB and NRF2, the reduction of COX-2 expression or the interaction with antiapoptotic pathways such as Bcl-2. Additionally, recently found that PPAR agonist treatment also increases catalase activity in the brain of an AD mouse model, suggesting an enhancement of the antioxidant capacity mediated by PPAR activation. It is possible to hypothesize that astrocytes, pericytes, and endothelial cells are able to respond in a similar way as has been observed for other cell types, including highly specialized cells (Zolezzi & Inestrosa, 2013).

IV. CONCLUSIONS

Currently, there is no effective therapy for AD. Therefore, a better understanding of the pathogenic events in AD could help to generate a more effective therapy that may interfere early in the development of the disease. Several studies have shown that the treatments with the peroxisome proliferators activated receptor-gamma (PPARγ) agonists known as thiazolidinedione drugs (TZDs), like pioglitazone, attenuate neurodegeneration and improve cognition in mouse models and patients with mild-to-moderate AD. Furthermore, studies on animal models have shown that pioglitazone facilitate amyloid-β plaque clearance, enhance mitochondrial function, and inhibit neuroinflammation.

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